

Appl. No. : 08/484,594
Filed : June 7, 1995

22. (Amended) A method for [the treatment of] of treating neuronal [degenerative diseases of] degeneration in the central or peripheral nervous system, comprising administering to a mammal suffering from said disease an amount of a prosaposin fragment effective to retard or halt neuronal degeneration, wherein said fragment includes the [neurotrophic activity of SEQ ID NO:1] active neurotrophic fragment located within amino acids 8-29 of SEQ ID NO: 3.

REMARKS

The specification has been amended to correct a SEQ ID NO: and to update the status of the parent application. The title has been amended to more accurately reflect the claimed invention. Claims 12, 18 and 22 have been amended. Accordingly, Claims 12-25 remain presented for examination. Applicants' representatives wish to thank the Examiner for the courteous personal interview conducted on October 25, 1996. In that interview, the undersigned discussed with the Examiner proposed amendments believed to advance the case toward allowance. The substance of the interview is incorporated into the foregoing amendment and the following remarks. Support for the claim amendments and new claims may be found in the original claims and throughout the specification. Reconsideration and withdrawal of the present rejections in view of the arguments and amendments presented herein are respectfully requested.

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Rejections under 35 U.S.C. § 112, first paragraph

The PTO objected to the specification and rejected Claims 12-25, stating that no disclosure was provided in the specification on "retarding or halting" demyelination nor neural degeneration. The PTO also contended that neither administration of the subject protein/peptides in an effective amount nor the effective treatment of any disease state. The PTO then discussed the numerous problems associated with treatment of such disorders.

In the specification, Applicants discuss the effective treatment of neuronal and myelination disorders by indicating disease states, routes of administration and dosages. The Declaration of John S. O'Brien, M.D., submitted herewith, establishes that prosaposin plays a key role in myelination, as mice lacking this protein exhibited severe hypomyelination (§7). Further, the Declaration states that the neurotrophic peptides reduced the death of myelinated Schwann cells and stimulated the production of sulfolipids specific to myelin (§6). Thus, it can reasonably be expected that prosaposin and active peptides contained therein will stimulate myelination and prevent demyelination.

The references and experiments discussed in the Declaration clearly show that by following the teachings in the specification, a person of ordinary skill in the art can effectively practice the method of the invention. Applicants disclose an "effective amount" of prosaposin or neurotrophic fragments thereof (0.1 to 1,000 µg/kg; Specification, page 10, last paragraph). The *in vivo* experiments disclosed in the cited references, as well as the experiments supported by the data enclosed herewith, all use concentrations of prosaposin/prosaposin fragments within this range and administer the proteins/peptides as discussed in the specification.

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The PTO stated that "administration" of neurotrophic factors requires solutions to not only bypass the blood brain barrier, but to selectively target responsive cells with enough trophic factor to maintain/preserved appropriate neural pathways. The PTO then focuses on the blood brain barrier issue, alleging that it was very doubtful whether any peptide other than the iodinated 18-mer shown in the specification could cross this barrier. Direct intravenous infusion of such peptides is only one contemplated mode of administration. The peptide can also be administered topically, intracerebrally or by direct injection into the cerebrospinal fluid, none of which require passage through the blood brain barrier for therapeutic efficacy. The PTO's skepticism regarding the ability of the subject neurotrophic factors to selectively target responsive cells with a high enough local concentration thereof is unfounded. As shown in the Declaration, the systemically administered peptides prevent hippocampal neuronal loss and significantly reduce diabetes and taxol-induced neuropathies. Thus, these factors clearly target responsive cells in a sufficient amount to prevent neural degeneration.

In regard to the blood brain barrier, the specification states that the 22-mer fragment, having a molecular weight of about 2600, would also be expected to cross the blood brain barrier and provides a reference in support of this statement. Moreover, the Declaration (§14) states that in addition to the 18-mer fragment exemplified in the specification, a 14-mer fragment encompassing the active neurotrophic region of prosaposin crossed the blood brain barrier.

The specification demonstrates not only the successful *in vitro* stimulation of neural cell outgrowth (Example 1), but also the *ex vivo* stimulation of myelination in mouse cerebellar

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explants (Example 2) by the use of the same peptides. The cell population of explants comprises a heterogeneous cell environment that mimics the *in vivo* environment. Thus, enablement of *in vivo* stimulation of myelination is supported by the specification. Example 7 is an *in vivo* experiment which demonstrates a biodistribution of an intravenously administered neurotrophic peptide consistent with *in vivo* access to neural tissues of the brain. These experiments indicate that those skilled in the art rely on *in vitro* efficacy to predict *in vivo* efficacy for these neuroactive peptides. The Barinage article cited by the Examiner discloses that IGF-1, BDNF and CNTF supported the growth of motor neurons in laboratory cultures (p. 772, Col. 3) and all three factors also aided the healing of injured rat motor neurons. On this basis, pharmaceutical companies initiated clinical trials. The *in vivo* efficacy of IGF-1 is echoed by Exhibit K and by John O'Brien (Decl. ¶12).

It is well known that NGF promotes neurite outgrowth in a number of cell types *in vitro* (see, for example, ref. B on PTO-1449). The *in vitro* neurotrophic activities of two agents, namely IGF-1 and NGF, correlate with *in vivo* efficacy in animal models relating to treatment of peripheral neuropathies.

The Declaration provides a more than sufficient showing of the efficacy of the claimed methods. The experiments discussed therein show that prosaposin and/or its neurotrophic fragments protect against neuronal cell death (¶8), increase the number of regenerating nerve fibers after nerve transection *in vivo* (¶8), and prevent diabetes-induced and taxol-induced neural degeneration *in vivo* (¶9). Further, both sensory and motor nerve conduction velocities were significantly improved in diabetic rats administered a neurotrophic fragment of prosaposin

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containing the active neurotrophic fragment located within amino acids 8-29 of SEQ ID NO: 3 (Decl. ¶10). Moreover, intrathecal administration of the 22-mer peptide (SEQ ID NO: 1) reversed allodynia in the Chung rat model (Decl., ¶11). These experiments were performed using similar parameters as those described in the specification (i.e., proteins/peptides, dosages, delivery methods, types of neural disorders). This post-filing date data is relevant because similar methods were used therein as were discussed in the specification. This data is not relied upon to enable the invention; instead, it merely confirms that the specification was enabling as of its filing date. Thus, the skilled artisan would have received sufficient guidance from the specification as originally filed to practice the invention as claimed without undue experimentation.

The large body of evidence presented herein clearly tips the scales in favor of enablement of methods of treating, preventing or slowing the progress of a neurodegenerative or myelination disorder. Regardless of the problems discussed in the art in treating neural degeneration, promoting neural protection and increasing myelination, it has clearly been shown that prosaposin and neurotrophic peptides derived therefrom can successfully accomplish these.

The PTO also stated that separation of an axon from its cell body invariably results first in the degeneration of the separated portion, then concludes that "retarding or halting neuronal degeneration" requires functional regeneration of axons already damaged followed by remyelination. The claims do not require complete treatment of all nerve injuries, only preventing or slowing neural degeneration. Thus, regeneration of nerve processes over long distances is not required. The present method will protect the vulnerable neuronal cells around

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the site of nerve injury. In essence, prosaposin and neurotrophic fragments derived therefrom can apparently rescue some of the surrounding neurons from cell death (Decl., ¶13). The subject proteins and peptides are also effective in partial nerve injuries or in demyelination disorders in which segmental demyelination of Schwann cells occurs, leaving the axons intact. These axons can be remyelinated by action of neurotrophic factors upon Schwann cells.

The PTO contended that the description of how the invention can be used to treat various disorders of the nervous system with an effective amount of prosaposin was lacking, and states that the specification does not address any of the causative factors associated with the other claimed neuropathological conditions. The instant claims are directed to preventing or slowing and treating such disorders, not to curing such disorders. Applicants realize that other causative factors play a role in the listed disorders; however, preventing or slowing such treatment by providing dosages and routes of administration which were successfully used in subsequent studies is reflected in the Declaration and accompanying references. This level of enablement is all that the law requires.

The PTO also stated that the specification did not teach which specific "fragments" or prosaposin constitute "functional neurotrophic fragments thereof," and determination of which peptides were neurotrophic would constitute undue experimentation. The claims have been amended to recite that the active neurotrophic fragment of prosaposin comprises amino acids 8-29 of SEQ ID NO: 3, or includes the active neurotrophic fragment located within amino acids 8-29 of SEQ ID NO: 3. This is the same language used in U.S. Patent No. 5,571,787. It was agreed upon at the interview that such language would be allowable.

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The PTO summarized by stating that due to the complexities regarding neuronal survival, growth, remyelination and administration of an effective amount of prosaposin/neurotrophic fragments, that undue experimentation would be required to practice the invention as claimed. To determine whether a specification is enabling, the factors to be considered are summarized in two leading decisions, Ex parte Forman 230 U.S.P.Q. 546,547 (Bd. Pat. App. Int. 1986) and In re Wands, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988). These factors are the quantity of experimentation necessary, the amount of direction or guidance presented, the presence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims.

As discussed hereinabove, the specification as filed would enable the skilled artisan to practice the invention without undue experimentation as evidenced by subsequent successful experiments using the same materials and the same techniques described in the specification. Accordingly, the specification provides sufficient direction or guidance for the skilled artisan to practice the invention as claimed. *In vivo* working examples are present in the specification. The nature of the invention is straightforward: the prevention and treatment of neural degeneration. The relative skill in the art of neurobiology was high at the time the application was filed. Thus, the skilled artisan would clearly be able to practice the invention as claimed in view of the specification as filed.

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Rejection under 35 U.S.C. § 112, second paragraph

The PTO rejected Claim 18, stating that the term "degradation-inhibiting fragment" was ambiguous. Claim 18 as amended no longer recites this term.

In view of the amendments and arguments presented herein, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. § 112, second paragraph.

Applicants submit that all claims are in condition for immediate allowance; however, if minor matters remain, the Examiner is invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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